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Dronedarone Is Superior to Placebo

The Case for Optimism

I read with interest the study by Piccini et al. (1) that evaluated dronedarone for treating atrial fibrillation (AF). I agree with the primary conclusion that amiodarone is more effective than dronedarone for maintenance of sinus rhythm, as would be expected on the basis of the DIONYSOS (Efficacy and Safety of Dronedarone versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation) trial (2). However, I have concern about the dronedarone data that might have mistakenly led to an overly negative appraisal of its effect.

In Figure 2A of the paper (1), the authors present an odds ratio plot for EURIDIS (EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maIntenance of Sinus rhythm) and ADONIS (American-Australasian trial with DronedarONe In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm) (3). The data as presented suggest that placebo had efficacy comparable to dronedarone in these studies, which directly contradicts the studies' conclusions. The answer to this inconsistency lies in the supporting data to the right of the odds ratio plot. For EURIDIS, the denominators of 411 and 201 patients/treatment arm come from the second line of Table 2 of the trial's publication (3). The numerators are supposed to represent the number of patients with recurrent AF and are also taken from Table 2, 5th line of data (1).

These numbers do not make sense as representing the number of patients with recurrent AF at 1 year. They would correspond to 74.7% (307 of 411) and 73.6% (148 of 201) with recurrent AF at 1 year for dronedarone and placebo, respectively, and thus would show no difference between the 2 treatments. The actual reported recurrence rates of AF at 1 year (Table 2, line 3 [1]) are 67.1% and 77.5% for dronedarone and placebo, respectively. Instead, I believe that the number of patients presented in line 5 of the table likely represents the denominator for the analysis that follows, much like the number of patients in line 2 also is a denominator, and absolute numbers of patients with recurrent AF are not specified, favoring presenting these data as percentages (1). It is also possible that the numbers in line 5 present some other subselection of the total patient population, but it is inconsistent with the results of EURIDIS to assume that they represent the number of patients with recurrent AF. The same number sources are used for ADONIS. This artificially makes dronedarone seem the same as placebo in terms of AF recurrence rate at 1 year, a finding that significantly differs from the data in Table 2 and the Kaplan-Meier plots in Figure 2 (3).

While awaiting clarification from the authors of EURIDIS and ADONIS, there seems to be an error here that creates an overly negative conclusion as to the effect of dronedarone. After all, dronedarone has already been demonstrated in several studies to be superior to placebo (3,4) and not equal to it, as is suggested by the article by Piccini et al. (1).

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Reply

We appreciate the opinions of Dr. Lewalter regarding our methodology (1), particularly the use of intention-to-treat populations. The meta-analysis was constructed with conservative assumptions to reduce the risk of type I error. From this perspective, when estimating potential differences among treatments, biases that make the treatments seem more similar (including crossovers or failure to receive treatment) are conservative assumptions. Intention-to-treat provides the best pragmatic estimate of a given therapeutic strategy (in this case, therapy with dronedarone vs. amiodarone) (2). Often disagreement arises over the exact definition of intention-to-treat in an individual trial. In our meta-analysis we attempted to include patients in the denominator according to treatment allocation at the time of randomization.

Although the primary end point in EURIDIS (EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maIntenance of Sinus rhythm) and ADONIS (American-Australasian trial with DronedarONe In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm) (3) was the time to recurrence of atrial fibrillation (AF), in our analysis the primary efficacy end point was recurrent AF at follow-up. This approach was